

NO DRAWINGS.

Inventor:—ROBERT RABINOWITZ.

Date of Application (No. 50638/67) and filing Complete Specification: 7 Nov., 1967.

Application made in United States of America (No. 592,728) on 8 Nov., 1966.

Complete Specification Published: 24 June, 1970.

1,196,049



Index at acceptance:—C3 P(8A, 8D2B3, 8K8, 8P1D, 8P1E1, 8P1X, 8P4C, 8P5, 8P6C, 8P6D, 8P6H, 8P6X); C2 C(20Y, 200, 30Y, 326, 366, 368, 79Y, 79X, 791, MC).

International Classification:—C 08 f 15/16

## COMPLETE SPECIFICATION.

## Alpha-Cyanoacrylate Ester Mixtures.

We, AMERICAN CYANAMID COMPANY, a corporation organised and existing under the Laws of the State of Maine, United States of America, of Berdan Avenue, Township of Wayne, State of New Jersey, United States of America, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

This invention relates to improved adhesive formulations for medical and veterinary use.

It is well-known to use an ester of  $\alpha$ -cyanoacrylic acid (hereinafter sometimes referred to as "a cyanoacrylate") for adhesive purposes. The rapidity with which these materials form tenacious bonds renders them extremely useful in most normal bonding applications and in many unusual ones as well. Perhaps the most notable utility of these adhesives resides in the field of human and veterinary medicine wherein it has been found they can replace conventional sutures as a means for closing the incisions made during the course of surgical procedures. The self-evident benefits derivable from this replacement stand in favor of the cyanoacrylates becoming a valuable addition to medicine's armamentarium. A cyanoacrylate adhesive for veterinary and medical use would have to satisfy several requirements, some of which are peculiar to this field and others of which must be met by adhesives in general. Thus, the adhesive must be capable of strongly and durably adhering the animal tissue involved. The adhesive must be usable under sterile condi-

tions. The viscosity should be such that the material does not run to unwanted areas. In the body, the material should be absorbable without toxic effect. Also, it should be non-irritating and non-necrotic to the contiguous tissue. Preferably, the adhesive should be storage stable for comparatively long periods.

Previous attempts have been made to provide cyanoacrylates satisfying these requirements. Thus, efforts have been made to provide cyanoacrylate formulations with a viscosity such that the material could be controllably applied from ordinary dispensing means, such as a tube or a squeeze-bottle. Two ways of doing this are described in U.S. Patent Specification No. 3,178,379. The first method involved dissolving a minor proportion of polymeric cyanoacrylate in the monomeric material. Such compositions are formed simply by mixing the monomeric cyanoacrylate with the desired polymeric viscosity regulator and with other ingredients normally used in such adhesives, such as a polymerization inhibitor, and thereafter agitating the mixture to achieve solution. While such mixtures have met with some success, they had certain limitations in respect to their clarity, stability and activity. Each of these qualities was somewhat lessened in the mixture of monomer and polymer as compared with the pure monomeric cyanoacrylate.

The second method which the patent describes involves dissolving a polymeric viscosity modifier (which may be one of many different polymers) in a solvent which is compatible with the monomeric cyanoacrylate. The solution of the polymer is then

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blended with the monomer and the solvent is then stripped from the mixture under vacuum. According to the patentee, this method of forming a thickened cyanoacrylate adhesive beneficially affects the latter's clarity, bulk stability and adhesive activity.

Another approach to the provision of a useful cyanoacrylate adhesive is described in our co-pending Application No. 49835/66 (Serial No. 1,123,360) and is based on the discovery that monomeric cyanoacrylate can be thickened to any desired extent without detracting from its adhesive capabilities by subjecting the monomer (free from significant amounts of free-radical polymerization inhibitors but stabilized against autopolymerisation by the presence of an anionic polymerisation inhibitor) to free-radical polymerization conditions to effect a partial polymerization whereby there is obtained a mixture of monomeric and polymeric cyanoacrylate having a viscosity at 25°C in the range of 50 to  $50 \times 10^5$  centipoises. To this is then added a free-radical polymerization inhibitor such as hydroquinone or butylated hydroxy toluene (2,6-di-t-butyl-p-cresol) to prevent thickening beyond the desired point. Such compositions have the advantage of dispensing with the need of mixing another polymer or a thickener into the cyanoacrylate monomer to obtain the desired viscosity.

In U.S. Patent 2,776,232, there is disclosed another method for obtaining improved general-purpose cyanoacrylate adhesives. According to the patentee, bonds of improved flexibility can be obtained by using a mixture of different monomeric cyanoacrylates as the adhesive material. Useful mixtures are prepared from any two alkyl cyanoacrylates or one alkyl cyanoacrylate and phenyl cyanoacrylate. Alternatively, the patentee describes making the desired mixture *in situ* by condensing formaldehyde with a mixture of cyanoacetates and depolymerizing the resulting mixture of polymers.

While the art has developed adhesive compositions which have good physical properties from the standpoint of strength of bond, activity, stability, viscosity, etc., further progress needs to be made in the development of adhesive compositions which also meet medical and veterinary requirements of surgically useful materials.

The adhesive composition in accordance with this invention comprises a mixture of (a) at least one ( $C_1-C_2$ ) alkyl  $\alpha$ -cyanoacrylate, and (b) at least one ( $C_4-C_{10}$ ) alkyl- or ( $C_4-C_{10}$ )cycloalkyl- $\alpha$ -cyanoacrylate, the concentration of component (a) being at least 3% but less than 25% by weight based on the total weight of components (a) and (b).

The uniquely useful compositions of this

invention may be used to adhere various animal (including human) tissue materials together. The materials to be bonded together are called the "adherends". The adherends may be the same or different materials and include such materials as animal flesh, bone, skin, muscle and nerve tissue, and the tissue of functional organs such as the spleen, the kidney, the liver and blood vessels. In use, at least one of the adherends is coated with the adhesive composition and the adherends are then contacted, if desired in the presence of an anionic polymerization initiator.

Preferably, the compositions of this invention will have 5—20 weight percent of the methyl and/or ethyl ester, and of these two esters it is preferred to use the methyl. The other ester component which forms the major portion of the adhesive composition used herein will have an alkyl or cycloalkyl group of four to ten carbons such as butyl, pentyl, hexyl, cyclohexyl or octyl. This invention also comprehends the use of mixtures of  $C_4-C_{10}$  alkyl or cycloalkyl esters along with methyl and/or ethyl  $\alpha$ -cyanoacrylate as above noted. Preferably, the compositions also contain conventional stabilizers to inhibit premature and undesirable free-radical or anionic polymerization.

The practice of the present invention affords several surprising and unexpected benefits since the cyanoacrylate mixtures used herein evidence qualities of their component materials often not in proportion to the quantities of the materials in the mixture. Thus, it is possible by proper choice of esters and concentration to use a small amount of a material which has both good and bad qualities, and find that a disproportionately small amount of the bad quality and large amount of the good quality carry over to the mixture. Thus, it has been found that certain cyanoacrylates, especially the methyl and ethyl esters show certain characteristics desirable for surgical use.

Methyl  $\alpha$ -cyanoacrylate shows relatively rapid tissue absorption and very rapid polymerization and tack times. Ethyl  $\alpha$ -cyanoacrylate shows somewhat slower absorption and slightly slower polymerization and tack times. Both materials yield thin, tough, transparent films.

It is also been found that  $C_4-C_{10}$  alkyl or cycloalkyl cyanoacrylates are desirable for surgical use because they show little evidence of macroscopic or microscopic inflammatory, toxic response. Though the methyl and ethyl cyanoacrylates are the esters of choice from the standpoint of tissue absorption, their surgical utility is restricted by relatively unfavorable tissue response. They, especially the methyl material, cause widespread tissue necrosis and undesirable inflammatory response. These reactions are

characterized by intense polymorphonuclear neutrophilic infiltration, death of tissue, proteinaceous coagulum membranes and focal abscess formations, delay in normal healing processes and immature fibro-connective tissue elaboration with attending widespread, thick, dense scar formation. The  $C_4$ — $C_{10}$  alkyl or cycloalkyl cyanoacrylates, as such, are surgically less desired than would be expected from their good tissue adhesive properties and lack of histologic response as above-noted, because of their slow tissue absorption and relatively poor film-forming characteristics.

As can be seen from the foregoing discussion, there are substantial shortcomings connected with the surgical use of only one alkyl cyanoacrylate regardless of which one is shown. Moreover, these shortcomings are not, surprisingly, avoided by using random mixtures of alkyl cyanoacrylates. Thus, the methyl and ethyl esters when used as a mixture do not complement each other from a standpoint of nullifying bad properties and reinforcing good properties. Likewise, use of two esters of the  $C_4$ — $C_{10}$  alkyl or cycloalkyl type is not a means of obtaining a surgically acceptable material. Thus, it is the recognition of two special groups of esters and the finding that at least one from each group must be used, which fundamentally underlies the present invention.

Typical mixtures for the practice of this invention contain methyl- and octyl  $\alpha$ -cyanoacrylates. These mixtures are rapidly polymerized, and are good tissue adhesives exhibiting good, tough films. These mixtures are not histotoxic, do not cause unacceptable inflammatory response, do not interfere with normal wound healing and are more rapidly absorbed than the higher molecular weight homolog alone.

The surgically acceptable adhesive mixtures of this invention are prepared by either mixing pre-formed cyanoacrylates of the two aforementioned categories or by forming said mixture by *in situ* preparation of the individual components. Generally, the technology involved is known to the art (for example, see U.S. Patent Specification No. 2,776,232) and the specific preparatory procedures do not constitute limitation on the present invention.

The adhesive mixtures of this invention can be packaged in any way which is suitable for dispensing adhesive materials under sterile conditions required for surgical use. The dispenser can be e.g., a syringe, tube, bottle or envelope. Dispensers fabricated from metals are preferred. Sterilization can be accomplished thermally by conventional means or by irradiation as disclosed in the aforementioned co-pending Application No. 49835/66 (Serial No. 1,123,360).

The adhesive compositions of this inven-

tion are uniquely useful for application as a coating to living tissue, animal or human, both external and internal, which through traumatic damage or surgical intervention, has bleeding surfaces. For example, in instances of lung damage or lung cancer it has been customary to remove the entire lung in order to provide a line of incision at which closure can be effectively accomplished. It is now found that the damaged portion may be removed and the present cyanoacrylic adhesive mixture used to coat the cut surface to stop bleeding (hemostasis) and form a new surface which in time will heal through natural processes and which meanwhile is protected from liquid loss or gaseous effusion so effectively that the damaged portion only, may be excised, and the remainder sealed off by the use of the adhesive mixture as sealant.

Similarly, in the instance of internal damage as for example if a liver or spleen is traumatically ruptured, as in an automobile accident or by some other cause, or if a portion must be removed with a cyst or for other reasons, the surface remaining can be coated with the present adhesive compositions to stop bleeding and a new surface effectively obtained. In the past, it has been generally necessary to approximate the remaining portions with sutures. The sutures, because of their cutting action through the soft tissue, cause a traumatic response and are difficult to use in soft friable tissue. With the use of the present adhesive, any shape of surface may be sealed, and a high percentage of functioning intact tissue retained. A coating of the present adhesive protects tissue, prevents bleeding, cuts down on liquid losses, and generally increases the flexibility of surgical procedures. The adhesive mixture can also be used to stop bleeding from small capillaries and larger blood vessels and to prevent oozing of blood and fluid from abraded skin surfaces.

In a particularly preferred aspect of the present invention, the specified mixed monomeric cyanoacrylates free of any weakly basic impurities (defining "base" as a proton acceptor), for example water or an alcohol, and essentially free of any free-radical polymerization inhibitors, but stabilized against anionic polymerization with a minor amount e.g. from 5 to 500 parts by weight per million parts of monomers, preferably from 10 to 250 ppm. of a Lewis Acid such as  $SO_2$ ,  $BF_3$  or  $HF$ , are partially polymerized by free radical initiation to give a mixture of materials having a viscosity of 50 to  $50 \times 10^6$  centipoises at  $25^\circ C$ . Free-radical polymerization can be initiated by conventional means. Thus, one can add to the monomer, essentially free of free-radical inhibitor, a conventional initiator such

as a peroxide (e.g., a benzoyl peroxide) or an azo compound (e.g., azobisisobutyronitrile) and the resulting mixture can be partially polymerized by conventional means to desired viscosity. Most desirably, an initiator is not added, but rather free-radical polymerization is initiated by means of thermal energy and/or various types of radiation. The thermal energy required to initiate free-radical formation can be conveniently obtained by heating the monomer mixture to a temperature above about 45°C. Alternatively, free-radical polymerization can be initiated by irradiating the mixture of monomers with U.V. light, X-rays, gamma-rays or electron rays.

An alternative method of obtaining an adhesive composition in the desired viscosity range of 50 to 50×10<sup>3</sup> centipoises at 25°C is to add a minor amount of a compatible polymeric material to the adhesive.

The following Examples are presented to further illustrate the present invention.

#### EXAMPLE 1

Nineteen grams of *n*-octyl  $\alpha$ -cyanoacrylate and 1.0 g. methyl  $\alpha$ -cyanoacrylate, each containing 50 p.p.m. of HF, were thoroughly mixed and, while contained in a 1 oz. polyethylene bottle, were irradiated with ultraviolet light until their viscosity was approximately 4,000 cps. Then 0.010 g. of butylated hydroxytoluene was dissolved into the solution to yield the final product.

In an identical manner, other mixtures of methyl and *n*-octyl  $\alpha$ -cyanoacrylate, as well as mixtures of methyl  $\alpha$ -cyanoacrylate with other C<sub>4</sub>—C<sub>10</sub> alkyl- and cycloalkyl  $\alpha$ -cyanoacrylates and ethyl  $\alpha$ -cyanoacrylate with C<sub>4</sub>—C<sub>10</sub> alkyl  $\alpha$ -cyanoacrylate were made, thickened, and stabilized.

#### EXAMPLE 2

A solution containing 15 g. of ethyl cyanoacetate, 135 g. of *n*-hexyl cyanoacetate, 75 g. of a 40% methanol solution of formaldehyde, and 50 g. of diphenyl phenylphosphonate, was heated to 80°C. and then 0.2 ml. of piperidine was added. The reaction mixture was maintained at 100°C. for 1 hour to complete the condensation. After 75 ml. of toluene was added, azeotropic distillation with the aid of a Dean Stark trap for 4 hours resulted in separation of the theoretical 17 ml. of water. Then 5.0 g. of phosphoric anhydride was added, the mixture stirred at 100°C. for 30 minutes, and then the toluene distilled off *in vacuo*. The viscous reaction mixture was then heated at 0.5 mm. under a short Vigreux column. A total of 85 g. of monomer were obtained over a pot temperature range of 160—200°C. This was redistilled at 0.5 mm.; 82 g. being recovered. Gas chromatographic analysis after the addition of 0.0041 g. of

HF revealed the presence of 12% by weight of ethyl  $\alpha$ -cyanoacrylate and 88% by weight of *n*-hexyl  $\alpha$ -cyanoacrylate. Forty grams of the product contained in a 2oz. polyethylene bottle were irradiated with ultraviolet light until the viscosity was approximately 10,000 cps. Then 0.041 g. of hydroquinone was added to provide stabilization against free radical polymerization. The product was then employed in a variety of surgical procedures.

Whereas mixtures of cyanoacrylates of this invention have a good combination of properties for surgical use, mixtures of lower esters (e.g., methyl and ethyl esters referred to as "M/E mixtures") or mixtures of higher esters (e.g., butyl and octyl esters referred to as "B/O mixtures") are not thus useful. For example, M/E mixtures show very rapid polymerization times; on the order of a few seconds. The tack times are also very rapid; practically instantaneous. The films formed are thin, smooth and transparent. Also, generally, these mixtures show good adhesive properties. Failing wounds occurs on the order of about 10—20%. But the M/E mixtures elicit, upon application to living tissue, a widespread acute inflammatory process accompanied by tissue necrosis and a proteinaceous coagulum membrane. They inhibit elaboration of hydroxyproline and generally, when in contact with living tissues, significantly prolong wound healing, and cause poor cosmetic results because of the inflammatory nature of the M/E mixture.

B/O mixtures also show rapid polymerization times on the order of ten seconds or less. Tack times are also very rapid (within a few seconds). As a skin adhesive they show good adhesive properties with failures of the order of about 5—10%. These mixtures cause, upon their application to living tissues, minimal acute inflammatory responses which do not interfere with normal wound healing. They show no inhibition of hydroxyproline elaboration and no definitive tendency to be absorbed. There is reduced incidence of intracytoplasmic polymer and the polymer generally shows no significant change in its optical properties. The films, however, are generally of very poor quality. They show considerable granulating efflorescence. In areas of high moisture such as the liver or spleen or other soft friable organs, they prove to be practically useless. Polymerization occurs so quickly and efflorescence is so extensive that there is no opportunity to spread the adhesive over the bleeding surface and hemostasis is not nearly as effective as with the preferred polymers particularly on organs such as liver and spleen which represent areas of high moisture.

### EXAMPLE 3

#### Coaption Tests

This Example shows the use of mixtures of cyanoacrylates of this invention, in dorsal open coaption tests. The purpose of this test is to determine the effectiveness of the adhesive in maintaining wound closure until gross and histologic healing take place.

In this test two six inch skin wounds are made on the dorsal lateral aspect of anesthetized rabbits. The depth of the incision is to the superior surface of the dorsal panniculus. Bleeding is carefully controlled in the standard manner. The adhesive is applied to the edges of the wound and the wound is reapproximated in as close to the original tissue plane as possible. Without benefit of bandage covering or stent, the animal is returned to the cage.

Observations are carried out for the first seven days at which time the animal is sacrificed. Data with respect to the characteristics of the closure are recorded both grossly and histologically. The measure of efficacy is established by a determination of the number and kind of wound failures encountered, grossly and histologically, in the total number of wounds repaired. A series of nine animals is used for each of the following adhesives:

1. Methyl  $\alpha$ -cyanoacrylate
2. Octyl  $\alpha$ -cyanoacrylate
3. 5% Methyl-95% octyl  $\alpha$ -cyanoacrylates

A summary of the data is noted below:

#### METHYL $\alpha$ -CYANOACRYLATE

*Polymerization Characteristics:* Tack time and polymerization times are very short. Positive closure is achieved within a period of a few seconds. The film is thin and transparent.

*Efficacy:* Seventy percent of the wounds are intact after seven days. The wounds edges are moderately raised and a thin escher is observed to slough from between the wound edges.

*Tissue Response:* The histological sections show an intense inflammatory response at those areas where adhesive came into contact with living tissue. Polymorph infiltration is widespread and there are areas of localized abscess formation. There is considerable necrosis proximal to the adhesive placement. In general, the response is identical to that mentioned elsewhere in this case. The wound edges are kept in place by the stenting effect of the dense eschar formed with the use of this adhesive material. Generally, reepitheliazation is not complete where this adhesive is used.

#### *n*-OCTYL $\alpha$ -CYANOACRYLATE

*Polymer Characteristics:* These are identi-

cal with those observed with methyl except that the film is a highly granular efflorescence.

*Efficacy:* Ninety percent of the wounds are intact after seven days. The wound edges are raised and a thin eschar is observed sloughing from between the wound edges.

*Tissue Response:* Generally, there is a low grade inflammatory response characteristic of early wound repair. There is considerable infiltration of young fibro-connective tissue throughout the sections observed. Reepitheliazation is complete but thinly developed under the slough. The wound edges are held together by normal progressive wound healing and by the stenting effect of the eschar.

#### 5% METHYL WITH 95% *n*-OCTYL $\alpha$ -CYANOACRYLATES

*Polymer Characteristics:* Tack time is generally delayed by a factor of about two, as compared with either individual component. Polymerization time generally is on the order of about 1 minute. The delay is advantageous because the operators are able to approximate the wound edges more carefully. The film formed is generally thin, tough, just slightly rough and semi-transparent.

*Efficacy:* Eighty to ninety percent of the wounds are intact after seven days. The wound edges are slightly raised and thin eschar is observed sloughing from between the wound edges.

*Tissue Response:* The tissue response was virtually identical with that seen with the octyl polymer after the seven-day interval.

### EXAMPLE 4

#### SPONGE IMPLANT TEST

An ideal method to determine toxicity and absorption properties of a liquid monomer which polymerizes to a solid is to absorb the liquid on an inert carrier material such as formaldehyde cross-linked polyvinyl alcohol sponges. The sponges are then implanted in animals and the effects of implantation observed by serial sacrifice at selected time intervals. Toxicity is determined by observing the effect of implantation on the surrounding tissue and by determining the extent to which the sponge is invaded by fibro-connective tissue. This latter can be observed microscopically but a more elegant method which also can be quantified is to determine the collagen content of the sponge by a determination of hydroxyproline, an amino acid characteristically found in collagen. Absorption can be determined by a loss in weight if fibroblastic activity is low (high toxicity) or by direct microscopic observation of a decrease in the amount of polymer by phagocytic action.

The animal most commonly used for the

implant test is the rat but other animals such as rabbits, guinea pigs, or dogs can be used. In a typical test, sponges are pre-weighed, and on two sponges a known weight of monomer is added. Physiological saline is added to two identical sponges to act as controls. All four sponges are then implanted in the ventral abdominal wall of a mature male rat just beneath the panniculus carnosus. Sponges containing the adhesive are commonly implanted in the upper and lower left quadrants and the controls in the upper and lower right quadrants. At sacrifice, all four sponges are removed; the upper quadrant sponges are dissected free of surrounding tissue, dried, weighted and subjected to analysis for hydroxyproline. The lower quadrant sponges are left with their surrounding tissue and are subjected to histological examination.

A series of ten animals is used for each of the adhesives noted in Example 3 with the following results:

#### **METHYL $\alpha$ -CYANOACRYLATE**

**Tissue Response:** Fourteen-day sponge implants show a widespread acute inflammatory response accompanied by widespread tissue necrosis and a proteinaceous coagulum membrane surrounding the sponge. There is no evidence of granulation tissue development at the implant site. The sections show generally little polymer within the sponge. That which is seen is amorphous in appearance and not light refractive. Hydroxyproline elaboration is markedly inhibited.

#### **n-OCTYL $\alpha$ -CYANOACRYLATE**

**Tissue Response:** Fourteen-day sponge implants show well-formed granulation tissue throughout the peripheral areas of the sponge. There are some areas which show granulation tissue at deeper sites. There is little evidence of inflammatory response. Foreign body giant cells are intimately associated with particles of implanted polymer.

There is generally little evidence of active polymer absorption in these sections although there are many areas which show polymer within the cytoplasm of foreign body giant cells. Most of the polymer is in the glassy platelike form. In those areas where polymer is closely associated with tissue elaboration, the polymer is more amorphous in appearance, i.e., it is serpingenous. Both forms of the polymer are light refractive. Hydroxyproline elaboration into the matrix of the sponge is consistent with development of granulation tissue and shows virtually the same hydroxyproline content as the saline controls.

#### **5% METHYL — 95% n-OCTYL $\alpha$ -CYANOACRYLATES**

**Tissue Response:** The development of granulation tissue and the over-all histologic pat-

tern for this mixture is very similar to that seen with octyl ester alone. There is evidence, however, that there is significantly more intracytoplasmic polymer which is presumably indicative of more rapid assimilation in the tissues.

Hydroxyproline elaboration is advantageously very similar to the results obtained with the octyl ester alone.

#### **WHAT WE CLAIM IS:—**

1. An adhesive composition comprising a mixture of (a) at least one ( $C_1$ — $C_2$ ) alkyl  $\alpha$ -cyanoacrylate, and (b) at least one ( $C_4$ — $C_{10}$ ) alkyl — or ( $C_4$ — $C_{10}$ ) cycloalkyl- $\alpha$ -cyanoacrylate, the concentration of component (a) being at least 3% but less than 25% by weight based on the total weight of components (a) and (b).
2. A composition according to Claim 1, wherein said mixture contains from 5—20% by weight of component (a).
3. A composition according to Claim 1 or Claim 2, wherein methyl  $\alpha$ -cyanoacrylate is used.
4. A composition according to any preceding Claim, wherein n-octyl  $\alpha$ -cyanoacrylate is used.
5. A composition according to any preceding Claim, containing also an anionic polymerization inhibitor.
6. A composition according to Claim 5 wherein said inhibitor is a Lewis Acid.
7. A composition according to any preceding Claim, containing also a minor amount of a compatible polymeric material whereby the viscosity of the adhesive composition is within the range of 50 to  $50 \times 10^5$  centipoises at 25°C.
8. A composition according to any one of Claims 1—6 which has been partially polymerized by free-radical polymerization whereby the viscosity of the adhesive composition is within the range of 50 to  $50 \times 10^5$  centipoises at 25°C.
9. A composition according to Claim 7 containing also a free radical polymerization inhibitor.
10. An adhesive composition, substantially as described in either one of Examples 1 and 2 herein.
11. A surgically useful article capable of dispensing sterile visious liquid materials and fabricated from a material free from impurities capable of initiating anionic polymerization, said dispenser containing an adhesive composition according to any preceding Claim.
12. An article according to Claim 11, wherein the dispenser is fabricated from a metal.
13. A method of joining tissue members of non-human animals, comprising coating at least one tissue surface with an adhesive composition according to any one of Claims 1—10, and contacting the surfaces to be

bonded whereby an adhesive bond is formed  
between said surfaces.

14. A method of effecting hemostasis in  
non-human animal tissue, comprising coat-  
5 ing the tissue with an adhesive composition  
according to any one of Claims 1—10.

TREGEAR, THIEMANN & BLEACH,  
Chartered Patent Agents,  
Melbourne House,  
Aldwych,  
London, W.C.2.  
Agents for the Applicants.

Printed for Her Majesty's Stationery Office by Burgess & Son (Abingdon), Ltd.—1970.  
Published at The Patent Office, 25 Southampton Buildings, London, WC2A 1AY  
from which copies may be obtained.

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